

REMARKS

Claims 33, 36 and 38-50 were pending. Claims 36, 43, 44, 46 and 47 are currently amended. No new matter is added. Applicants respectfully request reconsideration of the rejections.

Claims 33, 36 and 38-50 have been rejected under 35 U.S.C. 112, second paragraph. The recitation of "transcriptional response element" in Claim 33 has been amended in accordance with the Examiner's suggestion.

The numbers recited in Claims 43, 44, 46 and 47 have been clarified as kilobases, as set forth in the specification, for example at page 24, lines 15-23. The numbers in Claims 48-50 properly refer to nucleotides. Claim 36 has been amended to refer to nucleotides.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 33 and 38-42 have been rejected under 35 U.S.C. 102(a) as anticipated by Hallenbeck *et al.*, WO 96/17053. The Office Action states that Hallenbeck teaches a replication competent virus vector under control of the CEA regulatory sequence.

Applicants respectfully submit that the presently claimed invention is not anticipated by Hallenbeck *et al.* The present claims recite a replication competent adenovirus where a first adenovirus gene essential for replication is under the control of a CEA-TRE; and a second adenovirus gene is under transcriptional control of a cell-specific, tissue-specific or cancer-specific heterologous TRE. The disclosure of Hallenbeck *et al.* fails to teach an adenoviral vector wherein more than one heterologous TRE is used to control expression of a first and second adenovirus gene essential for replication.

The disclosure in Hallenbeck (WO 96/17053) includes a description of adenoviral vectors that contain a gene which is essential for replication, operably linked to a heterologous transcriptional regulatory sequence, such that replication is conditioned on the presence of a trans-acting transcriptional regulatory factor(s). The publication describes the adenovirus E1a OR E1b gene may be operably linked to a tissue-specific transcriptional regulatory sequence and a vector which encodes a heterologous gene product that is toxic for the target tissue.

While Hallenbeck *et al.* recite a variety of transcriptional regulatory sequences (with examples recited, including: carcinoembryonic antigen (CEA), DE3, alpha-fetoprotein (AFP), Erb-B2, surfactant, especially lung surfactant, and the tyrosinase promoter), there is no teaching or suggestion that greater specificity or unexpected benefits could be obtained from the use of two

different TREs to regulate a first and second adenovirus gene.

WO 96/17053 recites a hepatoma-specific promoter and an alpha-fetoprotein promoter, linked to E1a (Example 1), the breast cancer-specific DF3-Mucin enhancer (Example 2), the melanoma-specific tyrosinase promoter (Example 3), the colon cancer-specific CEA promoter (Example 4), and replacing the promoter of E2a in an adenoviral vector with a tumor specific promoter (Ex 1-4), alone or in combination with a gene such as TK, cytokines, or any therapeutic gene placed into the E3 region of the vector backbone by standard plasmid construction and homologous recombination under the control of an E1a-dependent promoter, or a constitutive promoter such as RSV or CMV (Example 5).

However, WO 96/17053 does not teach replication competent adenovirus vectors with two or more adenovirus genes essential for replication under control of two or more different heterologous cell-specific TREs that are functional in the same cell. The additional TRE and the heterologous feature, which features are recited in all of the claims of the present application, add unexpected advantages to the virus. The Patent Office has previously acknowledged in commonly owned patents, e.g. U.S. Patent no. 6,585,968; and U.S. Patent no. 6,436,394 that the prior art does not teach two different TREs in such an adenoviral vector.

Adenoviruses in which two adenoviral replication genes are controlled by two different heterologous TREs have been shown to have increased specificity. This unexpected benefit is not taught or suggested by the cited art.

Claims 36 and 43-50 have been rejected under 35 U.S.C. 103(a) as anticipated over Hallenbeck et al., in view of Richards et al. (WO95/14100). As stated in the Office Action, Richards et al. teaches a human CEA-TRE which is used to express heterologous genes. However, Richards et al. fails to remedy the deficiencies of Hallenbeck *et al.* The combined references fail to teach the use of heterologous promoters controlling a first and second adenoviral gene essential for replication, as set forth in the present claims.

In view of the above remarks, Applicants respectfully submit that the presently claimed invention is not anticipated or made obvious by the cited references. Withdrawal of the rejections is requested.

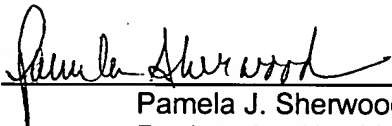
CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-007CON.

Respectfully submitted,

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